UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,170	01/04/2002	Arthur J. Chirino	A-69566-2/RFT/RMS/RMK	8567

7590 01/27/2005

Robin M. Silva, Esq.
FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP
Suite 3400
Four Embarcadero Center
San Francisco, CA 94111-4187

EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,170	CHIRINO ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

1. Amendment filed 10/18/2004 is acknowledged. Claims 1-31 are canceled. Claims 33-36 are added. Claims 32-36 are pending.

Applicant's arguments have been fully considered but were not deemed persuasive for the reasons stated below. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, first paragraph (new matter).

2. Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The new base claim 33 introduces new matter it uses phrase "inputting three dimensional coordinates of a target protein". There is no disclosure in the specification of inputting of all three dimensional coordinates of entire target protein (e.g., of a growth hormone). Rather, specification addresses inputting target protein's backbone structure, i.e., coordinates of the non-side chain atoms.

Claim Rejections - 35 USC § 112, second paragraph.

3. Claims 32-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In response to outstanding rejection under 35 U.S.C. 112, second paragraph, applicant submits that the rejections are obviated by replacing the now canceled base claims 24 with new claim 33. Although some of the rejections are now indeed moot, the following rejections are deemed necessary:

A. Claim 33 b): The term "target structure" is not clear and does not have antecedent basis. There was no "structure" to which protein design or "filters" can be applied; all that has been entered into computer are coordinates of protein (or, rather, coordinates of protein's backbone).

B. Claim 33 b.ii-iii. It is not clear what T cell epitopes are meant. According to specification, all that is being inputted into computer are 3-D coordinates of the target protein's backbone, i.e., a sequence of (-NH-CH-CO-) moieties stripped of side chains and, consequently of presence of any epitopes of the initial "target protein". In addition such backbone is further modified by applying steps of "protein design" and "immunofgenicity filter". Hence, as a result of all these method steps, the resulting "variant protein" will not be the related to the

originating "target" protein and it is not clear which "T cell epitopes" are being addressed. Also, it is not clear how an immunogenicity filter can "modify T cell epitope" where no T cell epitope is present.

C. Claim 33 b. iv). The term "plurality" does not have antecedent basis.

Claim Rejections - 35 USC § 112, first paragraph (written description).

4. Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to method of screening for proteins with altered immunogenicity. The proteins may be such as cytokines or growth hormones (claims 34,35) This rejection addresses an embodiment wherein the resulting variant protein have same biological function but altered immunogenicity (unlike embodiments that would yield unrelated protein structures - as was addressed in rejections under 35 U.S.C. 112, second paragraph, above).

There is no single example in the specification of the operability of the method neither *in silico,* nor in experimental conditions on a real protein synthesized following its *in silico* design. Specification contains only one mention of "immunogenicity filter" which is so vague that it is not clear whether applicant was in possession of any algorithm or scoring function that would result in a design of a protein with altered immunogenicity.

The inventor must be able to describe the item to be patented with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique method that makes it worthy of patent protection. The reader can certainly appreciate the goal but establishing goals does not make a patent. As the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993). To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; *see also Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"). There is no demonstration in the specification that applicants generated any compound which, after computer generation, and application of "computational immunogenicity filters" had immunogenicity different from that of parent molecule. Similarly to *In re Wilder*, 736 F.2d 1516 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 1209 (1985) the specification did "little more than outline] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."

None of sufficient physical and/or chemical properties were found in the specification. In regard to functional characteristics specification correctly states that a sequence can be optimized using computational methods and that numerous known computerized algorithms predict binding of peptides to MHC molecules.

Examiner does not dispute whether applicants were in possession of a method of determining binding to MHC molecules, however at issue is whether applicant was in possession of method of modulating immunogenicity. Discrepancy between predicted data on MHC binding and immunogenicity is well known. Thus, Meister et al. (i.e one of the methods used in the instant method) discusses that not all peptides predicted to bind to MHC peptides can be expected to stimulate immune response, both *in vivo* and *in vitro*. For example, only about one third (!) of peptides having motif corresponding to a given MHC allele have been found to interact with that MHC molecule. In some cases peptides which bind MHC molecules are immunodominant. See p. 598, second paragraph, and p. 582, second paragraph. Buus et al teaches that "there are still many examples of erroneous prediction of binding at the individual peptide level; furthermore, interaction at one subsite may affect interactions at other subsites" (see paragraph bridging pages 211-212).

Section 112, first paragraph, requires the patentee to "show that an invention is complete by disclosure of substantially detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the invention. Even if the inventors were reasonably certain that immunogenicity of target protein can be modified using claimed computational methods, there is no showing in the patent that they knew that to be a fact. There is no showing of a single embodiment demonstrating modified immunogenicity. The reader can certainly appreciate the goal but establishing goals does not make a patent. As was mentioned in the rejection, the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993).

Response to arguments

Applicants argue that they are in posessionb of method of determining binding to MHC molecules

Further applicant asserts that the accuracy of the references cited in the rejection is not 100%. Examiner is not clear about the relevance of accuracy of papers and its relation to patentability. If what is meant is accuracy of binding to MHC, Examiner maintains that the issue is not whether applicants were in possession of a method of determining binding to MHC molecules, but whether applicant was in possession of method of reducing immunogenicity by method steps designed to achieve this objective. Discrepancy between predicted data on MHC binding and immunogenicity is well known and addressed in the references discussed in the rejection. Further, there is nothing in the claims directed to MHC binding; the claims are drawn, in general, to screening for variants of any proteins.

Claim Rejections - 35 USC § 112, first paragraph (enablement)

5. Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as not being enabled.

First, in view of the concerns about ambiguity of the claims language expressed in the rejections under 35 U.S.C. 112, second paragraph, it is not clear how to make the invention as claimed. In particular, as there is no "target structure" entered (all that has been entered into computer are coordinates of protein or, rather, coordinates of protein's backbone) it is not clear to what a protein design or "filters" should be applied. Further, as all that is being modified

is a protein backbone, i.e., a sequence of (-NH-CH-CO-) moieties stripped of side chains (and, consequently of presence of any epitopes of the initial "target protein"), it is not clear how to make a protein having T cell epitopes of original target protein. Also, it is not clear how an "immunogenicity filter" has to be applied to "modify T cell epitope" where no T cell epitope is present.

Further, the lack of clear definition of "immunogenicity filter" precludes making the invention as claimed. Specification states that

"By "computational immunogenicity filter" herein is meant any one of a number of scoring functions derived from data on binding of peptides to MHC molecules, or T cell epitopes or B cell epitopes". Paragraph [0128].

No scoring functions to be used as an "immunogenicity filter" are described; all discussion of various scoring functions in the specification is related to computational protein design (claim 33, step b.iii). There is no single example in the specification of the operability of the method neither *in silico,* nor in experimental conditions.

Second, It is not clear how to use the invention as claimed. The method produces proteins that have both altered core structure and added other moieties (claim 33, step b.iii, "comprising" language). The latter can be from addition of several residues (p. 36, bottom) to addition of other large proteins which, obviously, will result in a protein having different functions and immunogenicity. In regard to alteration of the core structure, it, too, will be expected to change the functions of the target protein. This is because the peptide's structure is determined by the interplay of the hydrophobic/hydrophilic, steric and electrostatic forces among the linked amino acid residues and It is not possible to predict the

effect of replacing a single amino acid residue in a peptide's structure or bioactivity. Therefore, if replacing one or more residues in a peptide unpredictably alters its structure, this replacement also may alter bioactivity unpredictably.

Therefore, insufficient guidance exist in the specification to enable a person of skill in the art to practice the invention without the need for undue experimentation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Conclusion.

6. No claims are allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

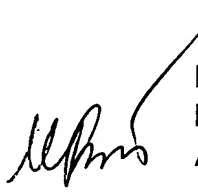
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will

the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571)272-0713. The examiner can normally be reached on 9 am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Michael Borin
Primary Examiner
Art Unit 1631

mlb